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General Summary and Conclusions

by DHEW Subcommittee on Health Effects of PCBs and PBBs *

Chemistry

The great complexity of PCB commercial mixtures has provided the difficult task of separating the components of these mixtures and determining the complete identity of the compounds. Efforts to define these mixtures have been quite successful over the past several years (*1*). Identification of the component chemicals in PCB residues presents another difficult problem. Little progress has been reported in this area. Since the fate of components of commercial PCB mixtures entering the environment cannot be followed directly, inferences must be drawn about chemical alteration of chlorinated biphenyl compounds in the environment mainly based on laboratory studies.

The known resistance of aryl chlorides to chemical oxidation and hydrolysis presumably was a major factor in the promotion of PCBs for industrial uses. Exposure to nonmetabolic environmental agents is unlikely to result in significant oxidation or hydrolysis of chlorinated biphenyls. However, since appreciable photoalteration of chlorinated biphenyls has been observed using either sunlight or sunlight-simulating lamps in the laboratory (*1*) as energy sources, it is highly probable that photochemical changes occur in the environment. These photochemical studies have indicated that reductive dechlorination to biphenyls of lower chlorine content is a predominant alteration route although formation of more polar compounds, including a chlorinated dibenzofuran, has also been reported (*1*, *2*). The diverse conditions of the environment make it difficult to predict accurately the end products and rates of photoalteration of chlorinated biphenyls. From a comparison of carbon–halogen bond energies, brominated biphenyls might be expected to be more readily altered by light than chlorobiphenyls. But because of the lower volatility and different end uses of bromobiphenyls, they may not be as readily exposed to light as the chlorinated analogs.

A typical PCB residue from fish resembles the Aroclor 1254 mixture more closely than it does other Aroclors (*3*, *4*). Considering the major components of Aroclor 1254 (*5*), it appears that penta-, hexa-, and heptachlorinated biphenyls tend to concentrate at this trophic level in the biosphere. It is of considerable interest, therefore, to carry out comparative accumulation, metabolism and toxicity studies emphasizing these higher chlorinated biphenyls using compounds of known chlorine substitution pattern. Individual chlorinated biphenyls are now quite accessible through synthesis and recent studies have begun to obtain these types of biological data.

Studies with the use of a group of five symmetrical hexachlorobiphenyl isomers in chicks (*6*) and in mice (*7*) indicated that distinct difference in toxicity are possible and these differences could be related to structure. The isomers with chlorine substituents in the 4,4′ positions appeared to accumulate more rapidly in adipose tissue and showed increased activity in the liver and greater overall toxicity (*6*, *8*). Comparison of two pentachlorobiphenyls in laying chicks again indicated the one isomer with 4,4′-substitution to have greater toxic effects (*9*, *10*). Structure-activity relationships, particularly for biphenyls known to be major components of commercial PCB mixtures, could be useful in assessing the potential hazard of these compounds.

* Members of the Subcommittee: A. C. Kolbye (Chairman), Food and Drug Administration, 200 C St., S. W., Washington, D. C. 20204; J. L. Buckley; J. Burke, F. Cordle; P. Corneliussen; D. Firestone; L. Fishbein; G. Flamm; G. F. Fries; A. Gardner; L. Garthoff; H. Gerstner; J. A. Goldstein; B. Hackley; C. F. Jelinek; L. Kasza; R. Kimbrough; T. E. Kopp; Y. Ku; R. L. Lehman; W. Marcus; H. B. Matthews; J. D. McKinney; J. McLaughlin; J. A. Moore; I. I. Pomerantz; R. A. Rhoden; J. A. Roach; S. Shibko; R. E. Shapiro; R. H. Teske; and W. Trotter.

A major part of determining human exposure to PCB residues in foods is evaluating the adequacy of the analytical methodology used and the significance of the data obtained. The methods applicable to PCB determination are complex and to be judged adequate should give acceptably reproducible results in the hands of experienced analysts. The degree of success of interlaboratory collaborative studies helps measure the adequacy of a method.

PCB residues are multicomponent mixtures. Many common chlorinated pesticides are extracted from samples along with the PCBs. Procedures for separation of PCB residues from interfering pesticides therefore become important as a prerequisite to quantitation. Several different quantitation techniques have been used (*1*). Comparison of PCB residue data is difficult where standardization of the quantitation procedure is lacking.

It has been shown that recovery of PCB mixtures purposely added to food samples, using commonly applied analytical methodology, varies with the average level of chlorination. Recoveries tend to decrease with increasing chlorine level (*11*).

Analytical procedures for determination of PCB and PBB (the latter is predominantly a hexabromobiphenyl) residues are essentially similar. They differ somewhat in cleanup of the extract and in the use of a higher column temperature for gas chromatographic determination of the PBB residue. The limit of quantitation for PCBs is generally 0.2 ppm for individual foods and about 0.05 ppm for total diet composites based on Food and Drug Administration methodology. For PBB residues, the limit of quantitation is approximately 0.05 ppm in fats and 0.01 ppm in nonfatty foods. Interlaboratory studies of analytical methods for PBB determination have not been reported.

The chlorinated dibenzofurans (Cl-DBFs) have become a focus of concern as the class of contaminant compounds in commercial PCBs most likely to contribute significantly to the toxicity of the PCB mixture. This concern presumably stems mainly from the demonstrated toxicity of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin and the similarity in structure between dibenzo-*p*-dioxin and dibenzofuran (*12*) and from the few toxicity data that have been published for Cl-DBFs (*13*). Recent data indicated the toxicity of 2,3,7,8-tetrachlorodibenzofuran approaches that of the analogous dibenzo-*p*-dioxin, at least in chicks and in guinea pigs (*14*). If the chlorinated dibenzo-*p*-dioxins can serve as an example, chlorinated dibenzofuran toxicity can be expected to vary with number and position of chlorine atoms on the parent ring system. Relationships between structure and toxicity will emerge as more Cl-DBFs are synthesized and tested for toxicity.

A range of Cl-DBFs (from dichloro through hexachloro) have been reported in various Aroclors (*15, 16*) and two specific compounds, the 2,3,7,8-tetrachloro- and 2,3,4,7,8-pentachlorodibenzofurans, have been identified (*17*). Quantitation of Cl-DBF contaminants in PCB mixtures, a difficult procedure, suggests total Cl-DBF levels in the low parts per million range (*16, 18*). The presence of Cl-DBF in a synthesized, individual, symmetrical chlorinated biphenyl has been reported (*19*). Chemical analysis of these individual chlorobiphenyls may be necessary prior to their use in toxicological and other biological studies.

There have been no published positive findings of Cl-DBFs in environmental samples or in foods other than rice oil. The finding of Cl-DBFs in such samples would not necessarily implicate commercial PCBs as the source of these contaminants, since Cl-DBFs (generally the higher chlorine levels) have been reported in other industrial chemicals (*20–22*). It is also possible that Cl-DBFs may be formed or altered in the environment.

Metabolism and Biochemical Toxicity

The effect of PCBs and PBBs on the hepatic mixed-function oxidase (MFO) enzymes has been the most thoroughly studied of any biochemical parameter that they are known to alter. On a molar basis, the PBBs are approximately fivefold more potent than the PCBs in inducing increased levels of the MFO enzymes (*23*). Among the PCBs it appears as if their potency increases with increasing chlorination and chlorine substitution in the *para* > *ortho* > *meta* positions respectively (*24*). However, this induction of the MFO enzymes is not unique to these compounds, and the induction observed is well within the range observed with many other xenobiotics. The PCBs are somewhat unique as MFO inducers in that they induce the formation of both Type I and Type II P-450 (*25*), but this induction may have been due to the fact that the commercial formulation used in the study was a mixture of twenty or more PCBs which were metabolized to an even greater number of metabolites. In addition, many, if not most commercial PCB formulations contain trace amounts of chlorinated dibenzofurans (*26*). These compounds may be up to 170 times more potent as MFO inducers than the PCBs. The chlorinated dibenzofuran concentration of American PCB formulations is usually quite low when they are produced; however, the effect of long-term exposure is unknown. In any case, since induction

of the MFO enzymes may result in increased hormone metabolism or carcinogen activation, exposure to the PCBs and PBBs should be limited on that basis alone.

PCBs and PBBs administered are relatively high concentrations, usually 50 ppm or higher in the diet, to laboratory animals have been shown to cause porphyria (*27*), disfunction of the thyroid (*28*), inhibition of various enzymes (*29*), changes in the liver to body weight ratios (*30*), various disorders of the liver (*31*), and to alter the level or utilization of corticosteroids (*32*), and vitamins A, D, and E (*33–35*). Certain of the less chlorinated PCBs have also been shown to have a mild estrogenic effect when tested in the immature rat and mouse (*36, 37*). However, most of these parameters have not been studied in sensitive species or demonstrated at low exposure levels in laboratory animals.

The available data imply that the PCBs and PBBs containing six or fewer halogen atoms are readily absorbed from the gut of higher animals. The available data also imply that the PCBs are not excreted to an appreciable extent prior to metabolism to more polar compounds, and that long-term PCB storage is in the skin and adipose tissue (*38*). Studies of PBB metabolism are not yet available. Since tissue samples from birds and mammals with known exposures to PCBs usually contain only those PCBs with five or more chlorine atoms, it is assumed that the less chlorinated PCBs have been metabolized and excreted. On the other hand, there is little evidence that fish can metabolize any PCB, and an analysis of fish tissue usually shows a PCB pattern very similar to that to which the fish were exposed (*11*).

Laboratory studies have demonstrated that the rate of PCB metabolism and thus excretion is approximately inversely proportional to the degree of PCB chlorination so long as there are two adjacent unsubstituted carbon atoms on the biphenyl molecule. When two adjacent unsubstituted carbon atoms are not present the biological half-life of the given PCB may be a matter of years and accumulation of high tissue concentrations with continued exposure is inevitable (*38*). It should be noted that the major constituent of FireMaster BP-6 does not have two adjacent unsubstituted carbon atoms and that the corresponding PCB has been shown to have an extremely long half-life in the laboratory rat and probably the human population as well.

It should also be noted that metabolism can also result in further complications of the PCB problem, because those PCBs which are most readily metabolized and excreted are those which are most likely to be metabolized via arene oxide intermediates. Whereas the reactivity of arene oxides varies greatly and often ultimately determines the toxicity, mutagenicity, or carcinogenicity of the parent compound (*39*), the PCBs offer such a range of degree and position of substitution that it would not be unlikely to find that one or more of these PCB metabolites would have the proper stability to be a mutagen or a carcinogen. Thus a move from the more highly chlorinated PCB formulations to the less chlorinated ones may help solve the long-term residue problem only to intensify other problems.

Animal Toxicology

Gleaning the information that is now available on animal toxicology makes it obvious that different commercial mixtures of PCBs elicit different toxic responses in animals, and that different animal species vary in their susceptibility to the toxic effects of PCBs. Reproduction is severely affected in mink at a dietary level of 5 ppm Aroclor 1254, and a slight effect is still noted at a dietary level of 1 ppm (*40*). In rhesus monkeys, reproduction was reduced at a dietary level of 2.5 ppm of Aroclor 1248 (*41*). In rats a dietary level of 20 ppm Aroclor 1254 depressed reproduction, while in the same rat strain (Sherman), in a study conducted simultaneously in the same laboratory, a dietary level of 500 ppm Aroclor 1260 was necessary to reduce reproduction (*42*). In comparative studies done with European products, Phenoclor DB6 and Clophen A60, and the American product, Aroclor 1260, the European products were more toxic to chickens than the American product (*43*). The difference in toxicity in this study was attributed to contamination of the European products with chlorinated dibenzofurans and perhaps chlorinated naphthalenes. However, if the differences in the effect on reproduction by the different Aroclors are compared, the contamination with chlorinated dibenzofurans may not be the decisive factor.

Hepatic porphyria has been produced in a number of species, namely the chicken, rabbit, Japanese quail and rat, by a number of commercial mixtures, such as Clophen A60, Phenoclor DP6, and Aroclors 1016, 1242, 1254, and 1260 (*27, 43–46*). Hepatic porphyria has not been reported in the monkey, mink, or human, which are species quite susceptible to the toxic effects of PCBs in other ways. Aroclor 1254 and Aroclor 1242 produced hepatic porphyria in the female rat at doses lower than Aroclor 1016. Again, different commercial mixtures produce this toxic effect at different dosage levels. The hepatic porphyria occurs concomitantly with an increase in ALA synthetase in the liver. Mixed function oxidases are also induced in the liver and comparative studies with PCB isomers have

suggested that if the 4,4′ positions on the biphenyl ring are occupied by chlorine atoms the effect is most pronounced (*47*).

The liver is the primary target organ for PCBs in the rat. Early changes include hepatomegaly, with a concomitant increase in smooth endoplasmic reticulum, lipid accumulation at higher dietary levels (20 ppm for Aroclor 1254 and 1260), and ultrastructural changes such as atypical mitochondria and the formation of "fingerprints" (concentrically arranged membranes surrounding lipid vacuoles) in the hepatic cytoplasm. An increase in mitotic figures and cell breakdown are increasingly noted with either higher doses or longer exposure (*48*). These changes are not as pronounced with Aroclor 1242 or 1016. Similar changes have been reported in the primate (*41*).

In the mouse, liver tumors have been produced with Aroclor 1254 (*49*) and Kanechlor 500 (*50*) and in the rat with Kanechlor 400 (*51*) and Aroclor 1260. Some tumors have also been produced with Aroclor 1242, 1254, and 1260 (*52*) in rats in a separate study. In one study with Aroclor 1260, some of the tumors were classified as hepatocellular carcinomas (*31*). The dietary levels of the PCBs in all of these studies were 100 ppm or more, a high level when compared to the daily average human intake of PCBs but not very high for subgroups with a high intake of fish from polluted waterways or in some occupational situations. This is emphasized by the fact that the dietary levels which produce tumors and the relatively low dietary levels which affect reproduction (2.5 ppm in the monkey and 1 ppm in the mink) of some commercial PCB mixtures do not represent a no-effect level. It is presently not known what the no-effect levels are. Other uncertainties contribute to these problems. The Yusho oil which caused a poisoning outbreak in Japan was not only contaminated with PCBs but also with high levels of chlorinated dibenzofurans.

In the primate, in addition to the effect on the liver, the gastric mucosa (*53*), the skin, and the Meibomian glands are also affected at comparatively low dietary levels and the bone marrow is depressed (*41*), while the gastric mucosa of the rat is affected only at exceedingly high doses (*49*). Whether the dog also shows an effect on the gastric mucosa needs clarification. In the rabbit, atrophy of the thymus is a toxic manifestation in addition to liver pathology (*44*). Fluid accumulation occurs in primates, chickens, and finches. The lymphatic system is also affected in minks.

The few studies conducted with some hexachlorobiphenyl isomers demonstrated that the 3,4,5,3′,4′,5′-hexachlorobiphenyl was the most toxic while 2,3,6,2′,3′,6′-hexachlorobiphenyl was the least toxic isomer (*7*). Penta-, hexa-, and heptachlorobiphenyls are preferentially retained in mammalian adipose tissue for extremely long periods of time (*48*) at fairly high concentrations in the rat for a recovery period of 16 months. Whether this has an influence on the toxicity of PCB mixtures has not been determined.

The toxic effects of the contaminants of PCBs have not been extensively studied. While it is assumed that chlorinated naphthalenes are toxic within the same dosage range as the chlorinated biphenyls, the chlorinated dibenzofurans probably have a greater toxicity. It is assumed that 2,3,7,8-tetrachlorodibenzofuran is the most toxic of this group of compounds. This compound also shows marked species variation. While the single oral LD_{50} in guinea pigs is between 5 and 10 μg/kg body weight, 1000 μg/kg TCDF given orally had no effect on rats. Mice are equally insensitive to the toxic effects of TCDF (*14*).

For the brominated biphenyls, limited toxicity data are only available on mixtures containing predominantly hexa- and octabromobiphenyl. Both mixtures differ sufficiently in isomeric composition so that their toxic effects may quantitatively be quite different and also different from the PCBs. Again, the problem of toxic contaminants has not been resolved. If toxic effects are similar to PCBs then, at least in some species such as mink and monkey, long-term low-level exposure should result in measurable toxicity. Additional animal studies are needed to resolve some of these problems. Poor metabolism and excretion of the brominated biphenyls may lead to long retention of these compounds predominantly in adipose tissue with accumulation to very high levels on continued exposure. Whether this would lead to sufficient recirculation of the chemicals to cause toxic effects on target organs is presently not known.

Human Exposure

Several reports (*54–61*) provide evidence that would indicate that a substantial proportion of the population of the United States has been exposed to PCBs. Minimal human exposure of the population to PCBs has occurred from food, air and water, while significant human exposure appears to be limited to sports fishermen consuming fresh water fish from contaminated streams and lakes, and to occupational exposure in industrial workers.

Jelinek and Corneliussen (*54*), in reviewing data from the FDA Total Diet Study (*62*), report that all food classes of the total diet declined to no PCB occurrences except in these meat-fish-poultry composites. About 40% of these composites continue to

contain detectable residues of PCBs, although only traces have been detected in the latter years. The fact that levels in these composites have declined to only traces further support the inference that the meat, poultry and eggs no longer contain detectable PCBs and that the low level findings are probably due to the fish in these composites. This would imply that the PCB levels in the diet may have "bottomed out" and may remain static until such time as there is a change in the PCB residues in fish.

Data compiled from studies sponsored by the National Marine Fisheries Service (NMFS) (*63*) also support the continuing presence of PCB residues in fish. A compilation of PCB data, representing the results of all the measurements known to NMFS on PCBs in fish used in the U. S. diet, indicates several important points: (1) while at one time or another, some PCB measurements have been made on many fish, there is an inadequacy of information on PCB residues in the most important fish items in the fish diet; (2) sampling and analysis have been sporadic and not designed to measure trends in human exposure; and (3) systematic surveys of neither the important items nor the species most likely to be contaminated have been undertaken.

However, these survey data do show that, in general, U. S. fish eaters include a wide variety of fish items in their diet and that some 93% of the U. S. population (197 million) consume fish, with the average annual consumption of fish being 15 lb/yr per person.

At present, it is difficult to estimate all human exposure to PCB from eating fish, either from the population as a whole or subgroups at higher risk of consuming large quantities of fish with higher PCB residues. Fragmentary evidence from NMFS data suggests that the exposure of the population as a whole from PCB residues in ingested fish is probably well below 19 μg/day per consumer, based on PCB levels which are estimated to be below 1 ppm for 19 g of fish consumed/day. This can be compared to the results of the FDA Total Diet Study, where it has been estimated that the overall PCB daily intake is on the order of 5–10 μg/day for the general population. The lower FDA estimate is based on the methodology of the Market Basket Survey where fish are purchased at the consumer level and would not be applicable to diets which include a high consumption of fish from certain areas with high PCB residues.

A recently completed study (*55*) has attempted to assess some of the consequences of human exposure to PCBs from the high consumption of fish from contaminated areas. The results of this study show that a group of sports fishermen consumed an average of 24-25 lb of fish/person/year, with the highest individual exposure for a 2-year period reported as 180 lb/yr. PCB residues in cooked fish ranged from 0.36 to 5.38 ppm. Although there was a wide range of blood PCB levels for each quantity of fish consumed, there was a highly significant correlation between the reported quantity of Lake Michigan fish consumed and the concentration of PCB in the blood of study participants, with the higher reported fish consumption being associated with higher PCB blood levels. The blood values ranged from a low of 0.007 ppm in the control group (fish consumption less than 6 lb/year) to a high of 0.366 ppm in the exposed group (fish consumption 24–25 lb/year).

These investigators calculated that the amount of PCB ingested by the exposed group could average 46.5 mg/year and ranged from 14.17 to 114.31 mg/year. While no systematic adverse health effects could be demonstrated in the exposed group when compared to controls, the investigators caution that any long-term chronic effects are unknown at the present time. Additionally, it can be concluded that exposure similar to those reported in this special group will continue and there is the likelihood that as sportsfishing becomes more popular, larger numbers of people may be exposed in a similar way.

Although human exposure to PCBs from air and water is probably minimal, there seems little question that such exposure does occur. Samples of ambient air collected in Florida, Mississippi and Colorado, show that PCBs were present at all locations. The average concentration at each of the three locations was approximately 100 ng/m^3 of air. Studies of surface water from the major drainage basins of the United States report the widespread occurrence of PCBs in both surface water and bottom sediments. Mean residue levels of PCBs in the surface water ranged from 0.01 to 0.05 μg/l., with a maximum residue level of 20.0 μg/l.

In Wisconsin, effluents from cooling water in aluminum foundries contained PCBs ranging from 11.5 to 335 ppb. Effluents from paper mills ranged from 0.01 to 25 ppb. Analysis of snow melt water from Wisconsin cities showed PCB residue levels of 0.17 to 0.24 ppb, suggesting that fallout of PCBs from the air may be an important source of PCBs entering the waters of the state.

In Michigan, testing of 900 samples of industrial effluents showed 22% had PCB residues > 0.5 μg/l., 8% > 1.0 μg/l., 6% > 10 μg/l., and 2% > 100 μg/l. With sludge disposal taking place by incineration, landfill and crop or pasture application, the continuation of PCBs in the environment seems obvious.

Adverse human health effects resulting from PCB

exposure have come primarily from studies of occupational exposure and from human exposure through the ingestion of contaminated rice oil in Japan.

Schwartz (*64*) provided some of the earliest reports of adverse health effects due to occupational exposure in the U. S., in which he described skin lesions and symptoms of systematic poisoning among workers who were reported to have inhaled chlorodiphenyls. There have been numerous reports over the ensuing years describing cutaneous eruptions and of systematic manifestations as well, among marine electricians, machinists, capacitor and transformer manufacturing workers, and others occupationally exposed to PCBs. The skin lesions described by Schwartz (*64*) in 1936 have come to be designated as "chloracne." Part of the chloracne lesion resembles adolescent acne, but is generally more severe and the lesion distribution is inconsistent with adolescent acne.

Hara (*65*) and Hasegawa et al. (*66*), have reported dermatologic ailments which include "brown chromodermatosis" of the dorsal joints of the hands and purple eruptions of the face and neck. However, Hasegawa et al. (*66*) performed a health survey of workers in carbonless copy paper factories, two years after the use of PCB in such processes had ceased, and reported no dermal effects nor liver function, urine or blood test abnormalities. PCB blood levels were reported as 0.01–0.02 ppm.

Typical clinical findings in the human exposure to PCB which occurred in Japan in 1968, and which resulted from the ingestion of rice oil contaminated with Kanechlor 400 included chloracne and increased pigmentation of the skin, increased eye discharge, transient visual disturbances, feeling of weakness, numbness in limbs and some disturbance in liver function. Adult Yusho patients had protracted clinical disease with a slow regression of symptoms and signs. In the dose-response epidemiologic study, the average cumulative intake of PCBs leading to overt symptoms was 2,000 mg, with the lowest dose leading to overt symptoms being 500 mg.

However, Kuratsune et al. (*67*) have introduced a new factor into the Yusho incidence with the finding that the rice oil contained chlorinated dibenzofurans (Cl-DBF) at 5 ppm. Nagayama et al. (*68*) report that the toxicity of (Cl-DBF) is said to be from 200 to 500 times that of PCB. Whether or not the (Cl-DBF) contaminant is the crucial toxic substance producing the symptoms observed in the Yusho incident, or whether the exposure to the high levels of Kanechlor 400 produced the observed effects, or whether there was an interactive process taking place is unknown.

The data necessary for determining reasonably accurate time and dose exposure to PBB in individuals in Michigan is either unavailable or nonexistent. Attempts to secure accurate dietary intake with the PBB levels in food and the duration of consumption have been unsuccessful. It is hoped that data to be received from the Michigan Department of Public Health may provide some basis for crude estimates.

While there appears to be no evidence at the moment to indicate acute health effects from exposure to PBB, any chronic effects remain largely unknown. A large-scale epidemiological study is expected to get underway shortly to identify all the farm family members from quarantined farms; a large group of study subjects secondarily exposed to PBB through the purchase of farm products on a regular basis from quarantined farms and a control group of individuals not exposed to PBB contamination. This study will continue efforts to identify any acute or chronic effects of PBB exposure through physical examination, biochemistry tests, and dietary histories. Efforts will continue to assess the original FireMaster BP-6 for the presence, if any, of chemical contaminants which might present human health hazards. In the meantime, a tenfold safety factor for PBBs when compared to PCBs appears both reasonable and acceptable based on all currently available scientific data.

Much work remains to be done concerning the toxicity of PCBs and PBBs and the association of these compounds with any demonstrable adverse human health effects.

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